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PATENT ABSTRACTS OF JAPAN

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(71)Applicant : ITO MIKIO

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(72)Inventor : ITO MIKIO

(54) AGENT FOR HEMORRHOIDS

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain an agent for the treatment of hemorrhoids, being safe even for a long period of administration and having cell-protecting action (antibacterial action, Maillard reaction inhibiting action, antiulcer action and wound healing action).

SOLUTION: A low-molecular chitosan having a molecular weight of 20,000-50,000 and a deacetylation degree of 90% is used at a relatively low concentration as a basic polysaccharide for the hemorrhoidal agent. A strong test cell protecting action and a wound healing action have been found by specifying the molecular weight of the physiologically active part of a low-molecular chitosan. The agent has an effect of reducing the administration dose by the use at a low concentration, a remedying effect on ulcerous part of hemorrhoids, an anti-inflammatory effect and an effect for suppressing the proliferation of sundry germs on the diseased part.

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CLAIMS

[Claim(s)]

[Claim 1] An agent for hemorrhoids diseases which makes an active principle 90% or more of chitosan whenever [molecular weight 20.000 - 50.000 deacetylation] [Claim 2] An agent for hemorrhoids diseases according to claim 1 characterized by using 90% or more of low-molecular chitosan by low concentration whenever [molecular weight 20.000 - 50.000 deacetylation]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] This invention relates to the agent for hemorrhoids diseases which makes an active principle low-molecular chitosan of molecular weight 20,000 - 90% or more of 50,000 deacetylation.

[0002]

[Description of the Prior Art] As basic polysaccharide, antibacterial and an antifungal action are known for many years, and, recently, chitosan has the report of an activity operation (JP,63-156726,A) of osteoblast, cancer transfer depressant action (JP,63-246332,A), a metallic complex and a chitosan organic-acid salt durability deodorant (JP,1-308565,A), and the agent for liver disease (JP,1-294627,A).

[0003] Moreover, it is known that a high concentration (2 - 8 % of the weight) medication method is effective in the therapy of **** accompanied by the atopic dermatitis of an inflammation sex skin skin disease, cutaneous sensitization, and the erythroderma, the chronic eczema, etc. (JP,2-289521,A).

[0004]

[The purpose of technical-problem **** invention which invention tends to solve] change of the epidermis accompanied by [in recent years] the hemorrhoids disease from diversification of meal culture and a constitutional abnormality in our country, coloring, change of hair, body odor (abnormalities in body odor by abnormality propagation of saprophytic bacteria, such as the side, a leg, opening, and body fluid), and a cause — unknown cold, the allergosis, a partial ulcer disease, etc. are increasing.

[0005] A hemorrhoids disease is a lesion produced from the rectum on the anus and the outskirts of it, and inside and external piles, an anal fistula, *****, a anal fissure, etc. are inflammation and a disease accompanied by an ulcer. Although anti-inflammatory activity is powerful if a suppository, the local anesthetic of an ointment gestalt, an antiphlogistic, an antibiotic, an antiallergic agent, adenocorticotrophic hormone, etc. are generally used in the case of the hemorrhoids disease, but it is in adenocorticotrophic hormone etc., granulation growth is controlled and the operation which delays wound healing is reported. For this reason, even if antibacterial, anti-inflammation, and the wound healing effect were high and carried out rear-spring-supporter use at the long period of time, an appearance of drugs with high safety was desired.

[0006]

[A means to solve a technical problem and to attain the purpose] this invention person discovered the place which actually carried out rear-spring-supporter use of the chitosan which does not almost have a side effect at the long period of time, and the very effective thing, in order to have experienced a hemorrhoids disease, pollinosis, and atopy ** and to attain the above-mentioned purpose also close relatives and himself. For this reason, as a result of inquiring about this quality and operating concentration (molecular weight etc.), it discovered that an effect was acquired enough by using low-molecular chitosan by 1% or less of low concentration 90% whenever [molecular weight 20,000 - 50,000 deacetylation]. Moreover, these effects find out the point in powerful cytoprotection (antibacterial, MERADO reaction inhibition, antiulcer, wound healing promotion), and came to complete this invention.

[0007] (Operation) this invention pharmaceutical preparation is a hemorrhoids disease therapy agent which has the test cell protective effect which makes an active principle 90% or more of low-molecular chitosan whenever [molecular weight 20,000 - 50,000 deacetylation], and the addition concentration in pharmaceutical preparation uses chitosan by 1% or less of low concentration.

[0008] The amount of adult used is 2 the affected part surface area of 1cm as external preparations, such as ointment, and suppositories. It hits. 100-200mg A degree (1 - 3% of epidermis concentration) is applied several times per day.

[0009] As operation activation stabilization support added by this invention material, saccharides, such as a lactose, cane sugar, and a dextrin, are used for hydroxypropylcellulose, the hydroxypropyl methylcellulose, albumin, etc. Moreover, in order to raise solubility and stability, as an inorganic-acid salt, an organic-acid salt, and a fatty-acid salt, use of a salt (it mainly uses together) with an acid antibacterial substance is also possible [salts, such as a hydrochloric acid, a sulfuric acid, a citric acid, amino acid, an ascorbic acid, the Reno Laing acid, an EPA acid, and DHA, are available, and] in order to heighten the propagation depressor effect of saprophytic bacteria further.

[0010]

[Embodiment of the Invention] Next, in relation to the example of manufacture, and the example of a drug effect pharmacological test, this invention is further explained to details.

The example of reference manufacture (purification of chitosan)

Shells, such as a crab and a shrimp, were processed with the alkali solution in the dilute-hydrochloric-acid list, and the chitin was manufactured by the calcium carbonate and deproteinization actuation. A profit slack chitin is heated by 80 - 120 °C in 40 - 45% sodium-hydroxide solution for 5 hours, N-deacetylation of a chitin is performed, and chitosan is obtained. By the reaction condition, a profit slack chitosan molecule can be prepared by the method of sorting out the thing of a macromolecule roughly with viscosity from low-molecular in process of deacetylation.

[0011] In addition, low-molecular chitosan pharmaceutical preparation of marketing in this invention example (5.2cp, molecular weight: viscosity of 0.5% solution : whenever [20,000 - 50,000 deacetylation] : 90.2%) [The Kimitsu chemical-industry incorporated company manufacture] was used.

[0012] The example 1 (oral pharmaceutical preparation - combination tablet) of pharmaceutical preparation It is 90% or more low-molecular chitosan 100 tetracycline hydrochloride whenever [deacetylation]. 10 magnesium stearates 1.8 hydroxypropylcellulose 2.5 milk Sugar ** Amount ** Amount 300.0mg Tablet (adult 1-time 3 lock one day 3 times recipe formula pharmaceutical preparation)

[0013] The example 2 (oral pharmaceutical preparation - single powder) of pharmaceutical preparation It is 90% or more low-molecular chitosan whenever [deacetylation]. 1000mg (adult let 500-2,000mg be the daily dose)

[0014] The example 3 (external preparations - ointment) of pharmaceutical preparation External preparations were prepared by the formula below.

Place It is a more than 90% low-molecular chitosan 100mg citric acid whenever [way deacetylation]. 100mg white vaseline 80g liquid paraffin 10g [0015] The example 4 (suppositories) of pharmaceutical preparation Suppositories were prepared by the formula below.

Place It is 90% or more low-molecular chitosan whenever [way deacetylation]. 1mg citric acid 1mg minocycline 10mg cacao butter 500mg or more was made once into the suppositories of a daily dose.

[0016] B) Drug effect pharmacological test (antiulcer, damage depressor effect)

The S.D system male rat with an effect ** experiment method weight of about 200g to a drug effect pharmacological test 1 ethanol gastric-mucosa failure is abstained from food before an experiment for 24 hours. Low-molecular chitosan (5.2cp, molecular weight: viscosity of 0.5% solution : whenever [20,000 - 50,000. deacetylation] : 90.2%) [Kimitsu chemical-industry incorporated company], Macromolecule chitosan (315cp, molecular weight: viscosity of 0.5% solution : whenever [500,000 - 1,000,000. deacetylation] : 82.0%) [Kimitsu chemical-industry incorporated company] and a chitin (viscosity: 40-mesh pass) [Kimitsu chemical-industry incorporated company] It suspended to gum arabic 1%, respectively, and administered orally to the rat. They are 1ml / 100g about dehydrated ethanol the 2 hours after. It administered orally by the capacity of weight and the stomach was extracted under anesthesia 1 hour after. The length of the damage which cut the stomach open along the large bay and generated stomach contents under observation with a stereoscopic microscope with an after [washing] micrometer at the gland stomach (mm) Width of face (mm) It measured and the product was made into damage area. And total of the damage area per animal was made into the damage characteristic.

[0017] ** Result low-molecular chitosan, macromolecule chitosan, and a chitin : in order to clarify a membrane defense operation of low-molecular chitosan, macromolecule chitosan, and a chitin, dehydrated ethanol was used as necrotic cell debris. Low-molecular chitosan 250,500 It reaches. 1,000 mg/kg By internal use, as compared with contrast, 87%, it reached 95% and the gastric-mucosa damage by dehydrated ethanol was controlled 99%, respectively (drawing 1). On the other hand, it is macromolecule chitosan. Similarly by internal use of 250 and 500 mg/kg, 64%, 83%, and a chitin are 250, respectively. And it is internal use of 500 mg/kg and gastric-mucosa damage was controlled 51% and 70%, respectively (drawing 1).

[0018] 2) Use an S.D. system male rat with a recovery effect ** experiment method weight [of an acetic-acid gastric ulcer] of about 230g, and it will let an experiment period pass from three days before ulcer inducement of feed intake time amount, and is 9:00-10:00 in the morning every day. And ~ 5:00 p.m. 6:00 It restricted in 2 hours. An acetic-acid gastric ulcer was made to cause according to Takagi's and others method by pouring an acetic-acid solution into the common wall of 0.05ml corpus-ventriculi section and a pyloric part of stomach from a chorion side 20%.

[0019] low-molecular chitosan, macromolecule chitosan and every day from the next day of acetic-acid impregnation of a chitin, and the morning — 8:00 and an afternoon — 5:00 minutes — up to 2 times and the 14th — administering orally — the 15th day — the recovery effect — Ito ** — histological mensuration estimated according to the method. That is, the stomach was extracted for the rat under anesthesia on the 15th, the organization was fixed with the neutral formalin buffer solution 10%, and the ulcer characteristic was measured under the stereoscopic microscope as mentioned above. Furthermore, histological mensuration estimated the degree of ulcer recovery in quest of ulcer section deficit area, the ulcer floor exposure reduction characteristic, and the membrane playback characteristic.

[0020] ** join ***** chitosan, macromolecule chitosan, and chitin:low-molecular chitosan 100,200 and 400 mg/kg a dosage — every day and two internal use — an ulcer characteristic — respectively — 21%, 49% and 60% (drawing 2), and ulcer section deficit area — respectively — 36% and 46% — and it was made to decrease 69% (drawing 3) Moreover, low-molecular chitosan is 100,200. It reaches. It reached 42% 19% and the membrane playback characteristic was made to increase an ulcer floor exposure reduction characteristic by 91% 27%, 52%, and 68% (drawing 4) by administration of a 400 mg/kgx 2/day, respectively (drawing 5). However, the dosage of a 100 mg/kgx 2/day did not show a significant operation to the ulcer characteristic and the membrane playback

characteristic.

[0021] On the other hand, by two internal use, macromolecule chitosan reached 23%, respectively and decreased an ulcer characteristic and ulcer section deficit area 34% every day [of 400 mg/kg]. Moreover, the chitin also decreased ulcer section deficit area 38%, and made the membrane playback characteristic increase by 47% by internal use of a 400mg/[kg] x 2/day (drawing 3 and drawing 5). However, the significant difference was not seen for the operation over the operation over the ulcer floor exposure reduction characteristic and membrane playback characteristic of macromolecule chitosan, the ulcer characteristic of a chitin, and an ulcer floor exposure reduction characteristic between contrast.

[0022] I asked for cooperation each to BORANTEA which is experienced in a use test recurrence nature gastric ulcer (H. pylori ulcer), BORANTEA which is experienced in recurrence nature gastritis, and one hemorrhoids disease BORANTEA, and had the ointment of the examples 3 and 4 of pharmaceutical preparation, and a suppository the chitosan presentation agent of the example 1 of pharmaceutical preparation used for hemorrhoids disease BORANTEA timely to H.pylori ulcer experience BORANTEA, and the questionnaire of the feeling of use was carried out.

[0023] as shown below, all the members of a result are good — the purport reply was carried out and there was no example of aggravation.

It is the reply [0024] of the purport which can expect the reply ** hemorrhoids disease borane tare effect of a purport which can expect the reply effect if there is also no generating of the BORANTEA ulcer relapse which is experienced in a reply result ** recurrence nature gastric ulcer (H. pylori ulcer), gastritis, etc. and it is normal. ** It became clear from the pharmacological test more than **, and use experience that the low-molecular chitosan of basic polysaccharide had powerful cytoprotection, an especially powerful gastric-mucosa protective action, and an ulcer recovery promotion operation. Chitosan is basic polysaccharide from which the acetyl group combined with the amino group of a chitin separated by adding NaOH to chitins (natural high molecular compound which acetylglucosamine combined 5000 or more), such as crab husks, 40 to 45% as mentioned above, and processing by 80 - 120 **C. A pressure decrease operation, the object for blood cholesterol level low lean crops, an immunity activation operation, an antibacterial action, etc. are already reported to chitosan, and it is sold to it as functional food etc. The amino group is related to the antibacterial action, pressure decrease operation, and decholesterolization operation of chitosan, and, generally it is molecular weight. 500,000-1,000,000 Macromolecule chitosan is used.

[0025] It is [whenever / this time and deacetylation] molecular weight at 82.0% whenever [deacetylation] in 90.2% about gastric-mucosa protection of the low-molecular chitosan of molecular weight 20,000-50,000, and the gastric ulcer recovery effect. 500,000-1,000,000 Comparison examination was carried out with the effect of macromolecule chitosan and a chitin. Consequently, the membrane protective action of the rat to dehydrated ethanol had the strongest low-molecular chitosan, and, subsequently was the order of macromolecule chitosan and a chitin. In the contrast rat, the bleeding sore was controlled almost completely by the rat which prescribed 500 or more mg/kg especially of low-molecular chitosan for the patient by administration in the stomach of dehydrated ethanol although the linear bleeding sore strong against the corpus-ventriculi section was produced.

[0026] Histological mensuration considered more the recovery operation of the rat acetic-acid gastric ulcer of low-molecular chitosan (100-400 mg/kgx2-/day) in details further this time. consequently, an ulcer characteristic (magnitude of an ulcer) and ulcer section deficit area (depth of an ulcer) — a dosage — it decreases anacritic — making — an ulcer floor exposure reduction characteristic and a membrane playback characteristic — a dosage — it was made to increase anacritic and the remarkable gastric ulcer recovery operation was shown. However, macromolecule chitosan and the recovery effect of a chitin (400 mg/kgx2-/day) were far weak compared with low-molecular chitosan. Although it must wait for future research about chitosan and the antiulcer action mechanism of a chitin, since chitosan has an amino group, at least, with a part, the chitosan dissolved in the acid within the stomach has compatibility in membrane, and the gastric-mucosa protective action of chitosan is considered to originate in the local action which carries out covering protection of the mucosal surface.

[0027] However, as compared with macromolecule chitosan and a chitin, as for a remarkable gastric ulcer recovery promotion operation of low-molecular chitosan, the absorption of this compound is mainly suggested. Although there is still no report and it is not clarified about the digestion of a chitin or chitosan, it is thought that depolymerize is carried out and it is absorbed with an enzyme called the chitinase and chitosanase which enterobacilli produces. So, low-molecular chitosan tends to receive enzyme-digestion as compared with macromolecule chitosan or a chitin, and is considered that an absorption coefficient is high.

[0028] H. An intractable ulcer recovers by disinfection of pylori, and although it is possible to reduce the relapse of an ulcer considerably, the method of disinfecting bacteria completely is not established yet. A protonpump inhibitor and an antibiotic are in vivo although an antibacterial action quite powerful in in vitro is shown. An effect is quite weak. The habitation part of bacteria is a mucus lower layer, and this can consider that shift of the drugs to the part is bad. Although the effect over H.pylori of chitosan still is not clear, there is the antiulcer effect which was excellent according to experience which this invention person's congeniality person took, and the effect over H.pylori is expected.

[0029] Furthermore, in the activity term of the chronic ulcer, or an intractable ulcer, since the amount of peroxy lipid in ulcer margin membrane is increasing, as for using together the material which has an antioxydation operation in chitosan, for example, a quercetin, a glutathione, tannin (catechin), ferulic acid, a tetracycline and the minocycline,

and the doxycycline, the synergistic effect of an antiulcer action or an H.pylori disinfection operation is expected. [Effect of the Invention] By making chitosan of molecular weight 20.000 - 90% or more of 50.000 deacetylation into an active principle, and using it by several% or less of low concentration, growth of epidermis, a recovery promotion operation, a hemostatic action, and a germicidal action are expected. Since safety is high and the antiulcer effect is strong to a long period of time even if it carries out rear-spring-supporter use, it is effective as a hemorrhoids disease therapy agent.

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] The effect of the low-molecular chitosan to an ethanol gastric-mucosa failure, macromolecule chitosan, and a chitin is shown.

[Drawing 2] The effect of the low-molecular chitosan to acetic-acid gastric ulcer recovery (ulcer characteristic), macromolecule chitosan, and a chitin is shown.

[Drawing 3] The effect of the low-molecular chitosan to acetic-acid gastric ulcer recovery (ulcer section deficit area), macromolecule chitosan, and a chitin is shown.

[Drawing 4] The effect of the low-molecular chitosan to acetic-acid gastric ulcer recovery (ulcer floor exposure reduction characteristic), macromolecule chitosan, and a chitin is shown.

[Drawing 5] The effect of the low-molecular chitosan to acetic-acid gastric ulcer recovery (membrane playback characteristic), macromolecule chitosan, and a chitin is shown.

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(54) 【発明の名称】 痔疾患用剤

(57) 【要約】

【目的】 長期間服用しても安全性が高く、細胞保護作用（抗菌作用、メイラード反応阻害、抗潰瘍、創傷治癒効果）を有する痔疾患治療剤を提供する。

【構成】 塩基性多糖類としての分子量 20,000～50,000 脱アセチル化度 90% 以上の低分子キトサンを比較的低濃度状態で使用する事を特徴とした痔疾患用薬剤である。低分子キトサンの薬理活性部分を分子量特定する手法により、強力な被殺細胞保護、創傷治癒作用を見出したものであり、低濃度で使用する事による投与量の削減効果、痔疾患潰瘍部分の修復効果、抗炎症効果、疾患部位の雑菌繁殖抑制効果を有する薬剤である。

【特許請求の範囲】

【請求項 1】 分子量 20,000～50,000 脱アセチル化度 90% 以上のキトサンを有効成分とする痔疾患用剤

【請求項 2】 分子量 20,000～50,000 脱アセチル化度 90% 以上の低分子キトサンを低濃度で、使用する事を特徴とした請求項 1 記載の痔疾患用剤

【発明の詳細な説明】

【0001】

【発明の属する技術分野】 本発明は分子量 20,000～50,000 脱アセチル化度 90% 以上の低分子キトサンを有効成分とする痔疾患用剤に係る。

【0002】

【従来技術】 キトサンは塩基性多糖体として抗菌、抗カビ作用は古くから知られており、最近では骨芽細胞の活性化作用（特開昭 63-156726）、癌転移抑制作用（特開昭 63-246332）、金属錯塩・キトサン有機酸塩持続性消臭剤（特開平 1-308565）、肝疾患用剤（特開平 1-294627）の報告がある。

【0003】 また、炎症性皮膚疾患のアトピー性皮膚炎、接触性皮膚炎、紅皮症を伴う乾癬、慢性湿疹等の治療に高濃度（2～8 重量%）投与方法が有効である事は知られている（特開平 2-289521）。

【0004】

【発明が解決しようとする課題及び発明の目的】 近年我が国では食文化の多様化から、痔疾患、体質異常を伴う表皮の変化、着色、毛髪の変化、体臭（脇・足・口・体液等の雑菌の異常繁殖による体臭異常）、原因不明の風邪、アレルギー疾患、局所潰瘍疾患等が増えている。

【0005】 痔疾患は直腸から肛門、その周辺に生ずる病変であり、内・外痔核、痔瘻、肛門炎、裂肛等、炎症、潰瘍を伴った疾患である。痔疾患の場合、一般的には坐薬、軟膏形態の局所麻酔剤、消炎剤、抗生剤、抗アレルギー剤、副腎皮質ホルモン等が使用されているが、副腎皮質ホルモン等にあつては抗炎症作用は強力ではあるが、肉芽増殖を抑制し、創傷治癒を遅延させる作用が報告されている。このため抗菌、抗炎症、創傷治癒効果が高く、長期間にわたり使用しても安全性が高い薬剤の出現が望まれていた。

【0006】

【課題を解決し、目的を達成する手段】 本発明者は、近親者及び自らも痔疾患、花粉症・アトピー症を経験しており、上記目的を達成するために、副作用が殆どないキトサンを実際長期間にわたり使用した所、極めて有効である事を発見した。このためこの品質（分子量等）と使用濃度について研究した結果、分子量 20,000～50,000 脱アセチル化度 90% 低分子キトサンを 1% 以下の低濃度で使用する事により、充分効果が得られる事を発見した。また、これらの効果が強力な細胞保護作用（抗菌、メラノイド反応阻害、抗潰瘍、創傷治癒促進）にある点を見

【0007】（使用方法） 本発明製剤は分子量 20,000～50,000 脱アセチル化度 90% 以上の低分子キトサンを有効成分とする被覆細胞保護効果を有する痔疾患治療剤であり、製剤中の添加濃度はキトサンを 1% 以下の低濃度で使用するものである。

【0008】 成人使用量は、軟膏等の外用剤、坐剤として患部表面積 1 cm² あたり 100～200mg 程度（表皮濃度 1～3%）が 1 日数回適用される。

【0009】 本発明材料に添加される作用活性化安定化担体としては、乳糖、ショ糖、デキストリン等の糖類が、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロースやアルブミン等が使用される。また、溶解性、安定性を高めるために無機酸塩、有機酸塩、脂肪酸塩として例えば塩酸、硫酸、クエン酸、アミノ酸、アスコルビン酸、リノレイン酸、EPA 酸、DHA 等の塩が利用可能であり、さらに雑菌の繁殖抑制効果をさらに高める目的で酸性抗菌性物質との塩（主に併用）の利用も可能である。

【0010】

【発明の実施の形態】 次に製造例、薬効薬理試験例に関連して本発明を更に詳細に説明する。

参考製造例（キトサンの精製）

カニ、エビ等の甲殻を希塩酸並びにアルカリ溶液で処理し、炭酸カルシウム、除蛋白操作によりキチンを製造した。得たるキチンを 40～45% 水酸化ナトリウム溶液中で 80～120℃ で 5 時間加熱し、キチンの N-脱アセチル化を行いキトサンを得る。得たるキトサン分子は脱アセチル化の過程で反応条件により、低分子から高分子のものを粘度により大まかに選別する方法で調製する事ができる。

【0011】 なお、本発明実施例では市販の低分子キトサン製剤（0.5% 溶液の粘度：5 cP、分子量：20,000～50,000 脱アセチル化度：90.2%）〔君津化学工業株式会社製造〕を使用した。

【0012】 製剤例 1（経口製剤～配合錠剤）

脱アセチル化度 90% 以上低分子キトサン 100

塩酸テトラサイクリン 10

ステアリン酸マグネシウム 1.8

ヒドロキシプロピルセルロース 2.5

乳糖 適量

全量 300.0mg 錠剤

（成人 1 回 3 錠 1 日 3 回 服用処方製剤）

【0013】 製剤例 2（経口製剤～単一散剤）

脱アセチル化度 90% 以上低分子キトサン 100.0mg

（成人 500～2,000mg を 1 日量とする）

【0014】 製剤例 3（外用剤～軟膏剤）

以下処方外用剤を調製した。

処 方

脱アセチル化度 90% 以上低分子キトサン 100mg

白色ワセリン	80 g
流動パラフィン	10 g

【0015】製剤例4 (坐剤)

以下処方で坐剤を調製した。

処 方

脱アセチル化度90%以上低分子キトサン	1 mg
クエン酸	1 mg
ミノサイクリン	10 mg
カカオ脂	5.00 mg

以上を1回分量の坐剤とした。

【0016】B) 薬効薬理試験 (抗潰瘍、損傷抑制効果)

薬効薬理試験

1) エタノール胃粘膜障害に対する効果

①実験方法

体重約200gのS. D系雄性ラットを実験前24時間絶食し、低分子キトサン(0.5%溶液の粘度: 5.2cp, 分子量: 20,000~50,000, 脱アセチル化度: 90.2%) [君津化学工業株式会社]、高分子キトサン(0.5%溶液の粘度: 315cp, 分子量: 500,000~1,000,000, 脱アセチル化度: 82.0%) [君津化学工業株式会社] およびキチン(粘度: 40メッシュパス) [君津化学工業株式会社] をそれぞれ1%アラビアゴムに懸濁しラットに経口投与した。その2時間後に無水エタノールを1ml/100g 体重の容量で経口投与し、1時間後にエーテル麻酔下において胃を摘出した。胃を大湾に沿って切開し、胃内容物を洗浄後マイクロメーター付き実体顕微鏡での観察下に腺胃部に発生した損傷の長さ(mm)と幅(mm)を測定し、その積を損傷面積とした。そして、一匹あたりの損傷面積の総和を損傷指数とした。

【0017】②結果

低分子キトサン、高分子キトサンおよびキチン・低分子キトサン、高分子キトサンおよびキチンの粘膜防御作用を明らかにするため、壊死性物質として無水エタノールを使用した。低分子キトサンは250、500 および 1,000 mg/kg の経口投与により、無水エタノールによる胃粘膜損傷を対照と比較して、それぞれ87%、95%および99%抑制した(図1)。一方、高分子キトサンは250及び500mg/kgの経口投与により、それぞれ64%および83%、またキチンは同じく250 および500mg/kgの経口投与で、それぞれ51%および70%胃粘膜損傷を抑制した(図1)。

【0018】2) 酢酸胃潰瘍の治癒効果

①実験方法

体重約230gのS. D. 系雄性ラットを使用し、飼料摂取時間を潰瘍惹起の3日前から実験期間を通して毎日午前9:00~10:00 および午後5:00~6:00 の2時間に制限した。酢酸胃潰瘍をTakagiらの方法に従って、20%酢酸溶液を0.05ml 胃体部と幽門部との境界壁に漿膜側から注入することにより惹起させた

チンを酢酸注入の翌日から毎日、午前8:00と午後5:00分に2回、14日目まで経口投与し、15日目に治癒効果を100%の方法に従い、組織学的計測法により評価した。すなわち、15日目にラットをエーテル麻酔下に胃を摘出し、10%中性ホルマリン緩衝液で組織を固定し、上述のように実体顕微鏡下に潰瘍指数を測定した。さらに組織学的計測法により、潰瘍部欠損面積、潰瘍底露出減少指数および粘膜再生指数を求め潰瘍治癒の程度を評価した。

10 【0020】②結果

低分子キトサン、高分子キトサンおよびキチン・低分子キトサンは100,200および400 mg/kg の用量で毎日、2回の経口投与により、潰瘍指数をそれぞれ21%、49%および60%(図2)、潰瘍部欠損面積をそれぞれ36%、46%および69%減少させた(図3)。また、低分子キトサンは100,200 および 400mg/kg×2/日の投与により潰瘍底露出減少指数を27%、52%および68%(図4)、粘膜再生指数をそれぞれ19%、42%および91%増加させた(図5)。しかし、100mg/kg×2/日の用量では潰瘍指数および粘膜再生指数に対して有意な作用を示さなかった。

【0021】一方、高分子キトサンは400mg/kgの毎日2回の経口投与により、潰瘍指数および潰瘍部欠損面積をそれぞれ23%および34%減少させた。また、キチンも400mg/kg×2/日の経口投与により、潰瘍部欠損面積を38%減少させ、粘膜再生指数を47%増加させた(図3および図5)。しかし、高分子キトサンの潰瘍底露出減少指数と粘膜再生指数に対する作用およびキチンの潰瘍指数および潰瘍底露出減少指数に対する作用は対照との間に有意差はみられなかった。

【0022】使用試験

再発性胃潰瘍経験(H. pylori潰瘍)のあるボランティア、再発性胃炎経験のあるボランティア、痔疾患ボランティア各1名に協力をおおぎ、H. pylori潰瘍経験ボランティアに対しては製剤例1のキトサン組成剤を、痔疾患ボランティアには製剤例3、4の軟膏、坐薬を適時使用してもらい、使用感をアンケート調査した。

【0023】結果は以下に示すように全員が良好な旨回答し、悪化例はなかった。

40 回答結果

①再発性胃潰瘍経験(H. pylori潰瘍)のあるボランティア潰瘍再発、胃炎等の発生もなく異常はないと回答効果が期待できる旨の回答

②痔疾患ボランティア

効果が期待できる旨の回答

【0024】考 察

以上の薬理試験及び使用経験から塩基性多糖体の低分子キトサンは強力な細胞保護作用、特に強力な胃粘膜保護作用と潰瘍治癒促進作用を有することが判明した。キト

サミンが5000以上結合した天然の高分子化合物)に40~45%NaOHを加え、80~120°Cで処理することによりキチンのアミノ基に結合したアセチル基がはずれた塩基性多糖体である。キトサンにはすでに血圧低下作用、血中コレステロール低下作用、免疫賦活作用、抗菌作用などが報告され、機能性食品等として発売されている。キトサンの抗菌作用、血圧低下作用および脱コレステロール作用にはアミノ基が関係しており、一般的には分子量500,000~1,000,000の高分子キトサンが使用されている。

【0025】今回、脱アセチル化度90.2%で分子量20,000~50,000の低分子キトサンの胃粘膜保護および胃潰瘍治癒効果を脱アセチル化度82.0%で、分子量500,000~1,000,000の高分子キトサンおよびキチンの効果と比較検討した。その結果、無水エタノールに対するラットの粘膜保護作用は低分子キトサンが最も強く、次いで高分子キトサン、キチンの順であった。対照ラットでは無水エタノールの胃内投与により、胃体部に強い線状の出血性びらんを生じたが、特に低分子キトサンを500mg/kg以上投与したラットではほとんど完全に出血性びらんが抑制された。

【0026】今回さらに低分子キトサン(100~400mg/kg×2/日)のラット酢酸胃潰瘍の治癒作用を組織学的計測法により、より詳細に検討した。その結果、潰瘍指数(潰瘍の大きさ)、潰瘍部欠損面積(潰瘍の深さ)を用最依存的に減少させ、潰瘍底露出減少指数や粘膜再生指数を用量依存的に増加させ、著しい胃潰瘍治癒作用を示した。しかし高分子キトサンおよびキチン(400mg/kg×2/日)の治癒効果は低分子キトサンに比べてはるかに弱かった。キトサン、キチンの抗潰瘍作用機序に関しては今後の研究を待たねばならないが、キトサンはアミノ基を有しているため、キトサンの胃粘膜保護作用は少なくとも一部分、胃内で酸に溶解したキトサンが粘膜に親和性を持ち、粘膜表面を被覆保護する局所作用に起因しているように思われる。

【0027】しかし、高分子キトサンおよびキチンと比較して、低分子キトサンの著しい胃潰瘍治癒促進作用は主として本化合物の吸収作用が示唆される。キチンやキトサンの消化吸収についてはまだ報告がなく、明らかにされていないが、腸内細菌の産生するギチナーゼやキト

サナーゼという酵素により、低分子化され吸収されると考えられている。それ故、低分子キトサンは高分子キトサンやキチンと比較して酵素的消化を受けやすく、吸収率が高いと考えられる。

【0028】*H. pylori*の除菌により難治性潰瘍が治癒し、潰瘍の再発をかなり低下させることは可能であるが、本菌を完全に除菌する方法はまだ確立されていない。プロトンポンプ阻害剤や抗生剤はin vitroではかなり強力な抗菌作用を示すがin vivoでの効果はかなり弱い。これは本菌の生息部位が、粘液下層であり、その部位への薬剤の移行が悪いことが考えられる。キトサンの*H. pylori*に対する効果はまだ明らかではないが、本発明者の親近者が服用した経験によれば優れた抗潰瘍効果があり、*H. pylori*に対する効果が期待される。

【0029】さらに、慢性潰瘍の活動期や難治性潰瘍では潰瘍辺縁粘膜での過酸化脂質量が増加していることから、キトサンに抗酸化作用を有する物質、たとえばクエルセチン、グルタチオン、タンニン類(カテキン)、フェルラ酸や、テトラサイクリン、ミノサイクリン、ドキシサイクリンを併用することは抗潰瘍作用や*H. pylori*除菌作用の相乗効果が期待される。

【発明の効果】分子量20,000~50,000脱アセチル化90%以上のキトサンを有効成分とし数%以下の低濃度で使用する事により、表皮の増殖、治癒促進作用、止血作用、殺菌作用が期待される。長期間にわたり使用しても安全性が高く抗潰瘍効果が強い事から痔疾患治療剤として有効である。

【図面の簡単な説明】

【図1】エタノール胃粘膜障害に対する低分子キトサン、高分子キトサン、キチンの効果を示す。

【図2】酢酸胃潰瘍治癒(潰瘍指数)に対する低分子キトサン、高分子キトサン、キチンの効果を示す。

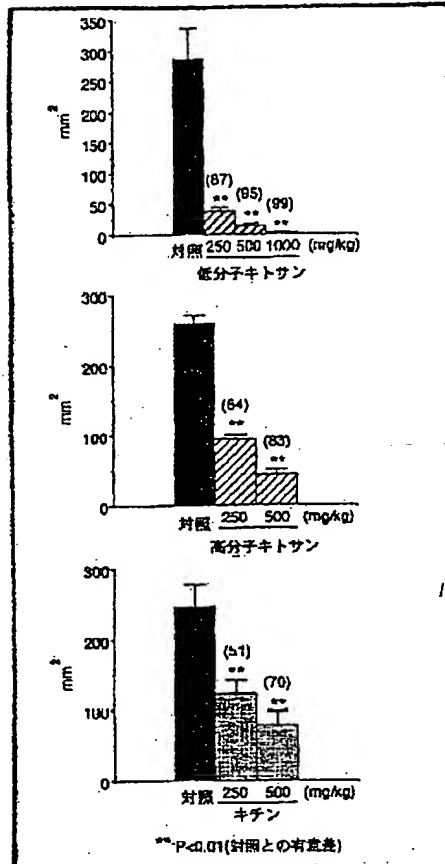
【図3】酢酸胃潰瘍治癒(潰瘍部欠損面積)に対する低分子キトサン、高分子キトサン、キチンの効果を示す。

【図4】酢酸胃潰瘍治癒(潰瘍底露出減少指数)に対する低分子キトサン、高分子キトサン、キチンの効果を示す。

【図5】酢酸胃潰瘍治癒(粘膜再生指数)に対する低分子キトサン、高分子キトサン、キチンの効果を示す。

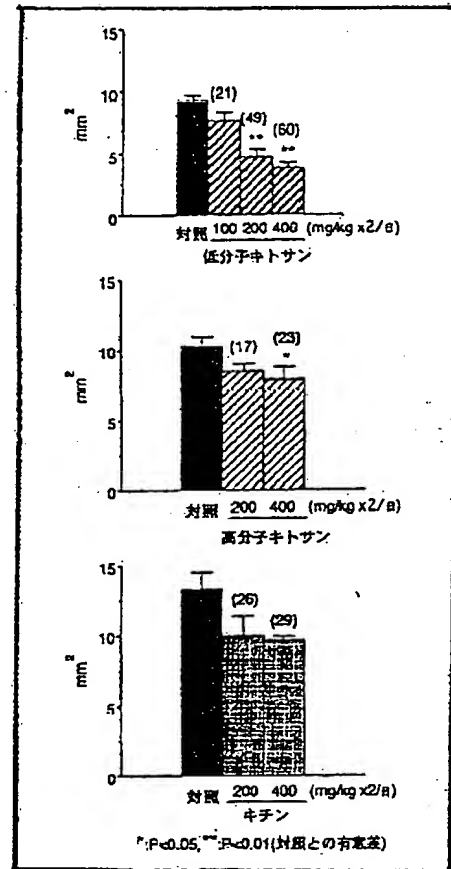
【図1】

損傷指数

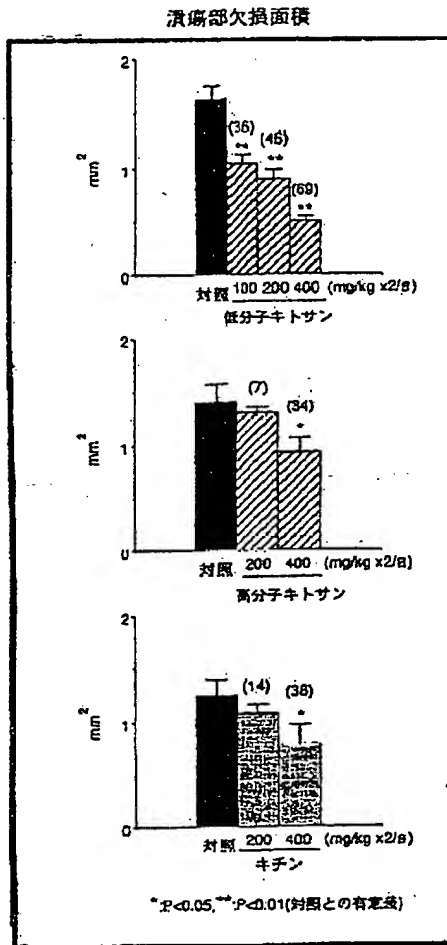


【図2】

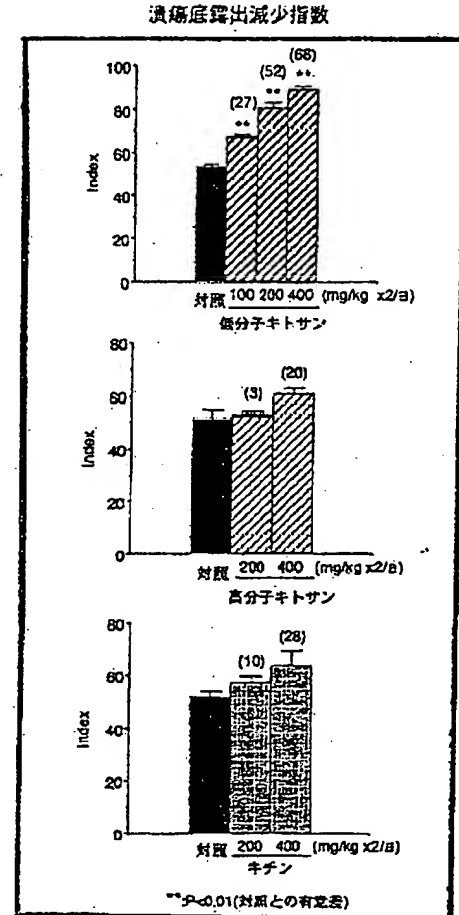
潰瘍指数



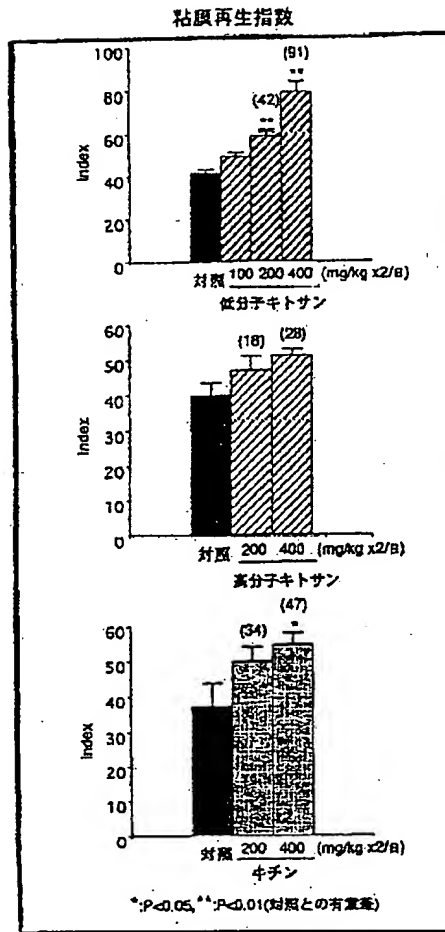
【図3】



【図4】



【図5】



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